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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/578,839	05/10/2006	Yeon-Soo Kim	Q94769	2219

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EXAMINER	
HORNING, MICHELLE S	

ART UNIT	PAPER NUMBER
1648	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/578,839	KIM ET AL.	
	Examiner	Art Unit	
	MICHELLE HORNING	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 4, 6, 8-10* is/are rejected.

7)☒ Claim(s) *2, 3, 5, 7* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *5/10/2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/10/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is responsive to communication filed 5/17/2007. The status of the claims is as follows: claims 1-10 are pending and under current examination.

Information Disclosure Statement

The information disclosure statement filed 5/10/2006 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered. US Patent 6033905 has been considered; however, the non-patent literature has not because no copies were submitted.

Comment [BC1]: You must consider the US patent. Line through the others and explain why.

Drawings

The drawings are objected to because the drawings, particularly Figures 5 and 6, are so blurred that they fail to depict anything useful; note that Figures 5 and 6 are suppose to show something in the empty lanes (see pages 4-5 of the instant specification). Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as “amended.” If

a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Comment [BC2]: There is no figure 13. Some of these don't look so bad - a western blot never looks like much of anything. Now if we are supposed to be seeing something in those empty lanes, that is another story.

Specification

The disclosure is objected to because of the following informalities: chimeric is incorrectly spelled as "chimaric" (see page 1, 1st paragraph).

Appropriate correction is required.

The use of the trademarks, including KODAK BIOMAX MR and LIPFECTAMIN, has been noted in this application; see pages 15 and 16 for examples. All trademarks, including noted examples, should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 10 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC

1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill of those in the art</u>

The invention relates to an anti-cancer agent comprising the chimeric ligand and a pharmaceutically acceptable carrier.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain). As illustrative of the state of the art, the examiner cites Sausville *et al.* (Cancer Research, 2006, vol. 66, pages 3351-3354) and Johnson *et al*. (British J. of Cancer, 2001, 84(10):1424-1431).

Sausville *et al.*, cited for evidentiary purposes, teaches that traditionally explored tumor model systems are insufficient to predict how actual human beings will respond to treatment in the clinic (page 3351, left column). Even when drugs with evidence of anticancer activity in preclinical *in vivo* models are given their maximum tolerated dose in humans, they frequently fail to produce useful activity in humans (*id.*). Also, with

regard to unpredictability, Johnson *et al.*, also cited for evidentiary purposes, teach that the *in vivo* activity of 39 different agents in a particular histology in a tumor model did not correlate to activity in the same human cancer. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. Further, the mode of action of anticancer agents is often unknown or very unpredictable and administration of such agents is often accompanied by undesirable side effects.

These articles plainly demonstrate that the art of treating cancer, particularly in humans, is extremely unpredictable, particularly in the case of a single compound or genus of compounds being used to treat any and all cancers.

2. The breadth of the claims

The claim is drawn to any and all possible fusion polypeptides comprising a ScFV specific for TAG72 and GaLV gp. Further, the claim is extremely broad insofar as it is drawn to the treatment of any and all possible cancers.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular administration regimens (*e.g.*, dosages, timing, administration routes, etc.) necessary to treat all of the various cancers claimed, particularly. The specification demonstrates a target cell specific infection of retrovirus expressing the ScFv-GaLV Env GP chimeric ligand using cell lines (pages 18-22). Pages 24-26 provide discussion of lung nodules in

mice induced by intravenous injection of TAG72 positive LS174T. Table 3 provides the differential effects of the chimera in lung metastasis models induced by either a TAG72 positive or TAG72 negative cell line. What is “dying” in Table 3? This is not clear. The number of cells? Can lung nodules die? In sum, the presented data merely shows the specificity of TAG72 targeting of cells and the efficiency of its transduction. The LS174T is a colon cancer cell line that induced lung metastasis in mice. While Applicants provide *in vivo* and *in vitro* results, it is not clear how the results are even related to an anti-cancer composition; it is noted that the supporting Figures are so poor in quality, they fail to depict the results. There is no guidance in the specification that provides a correlation of treating LS174T-induced metastasis to clinical efficacy. The specification provides no support for an anti-cancer composition.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed compound could be predictably used as a treatment for any and all cancers.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable” (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that because the instantly claimed compound can target TAG 72, *a priori*, be useful as an anti-cancer composition. While the claims are broad with respect to type of cancer, Applicants only provide one working example in a mouse model.

Determining if any particular claimed compound would lead to anti-cancerous effects would require subjecting it to clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants. As noted *supra*, even *in vitro* and *in vivo* assays do not always correlate to efficacy in humans and are not generally predictive of clinical efficacy.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim 7 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the *Wands* factors.

Nature of the invention. Claim 7 is directed to a specific recombinant expression vector, pHEFvGEL199. The Accession No: KCTC-10596BP.

State of the art. See rejection below. Briefly, the art teaches both TAG72 and GaLV env glycoprotein. Also, the art discloses using GaLV env gp to target cells and subsequently lead to cellular death.

Scope of the claims. The claim is specific regarding an expression vector.

Guidance of the specification. The specification provides some guidance regarding making this vector (see page 14); the disclosure fails to state that the material will be maintained in the deposit facility and any restriction for obtaining the material will be irrevocably removed upon granting of a patent.

Predictability in the art. Predictability would be impossible for the skilled artisan given the teachings.

Working example. The working examples demonstrate the expression and the use of the vector (see Example 1).

Given the analysis above, there is undue experimentation for the ordinary artisan. While some guidance is provided regarding the structure, the working examples provide specific functions for this vector. The skilled artisan would be required to correlate the structure to the specific functions, requiring undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6, 8 and 9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fielding et al (2000) and Goel et al (2000).

Fielding et al describe a hyperfusogenic Gibbon ape leukemia envelope glycoprotein and its targeting by ligand display (see whole document). The authors describe the ability of this protein to induce cell-cell fusion which leads to subsequent cell death following the transfection of a GaLV envelope glycoprotein lacking an R peptide in human cells (GaLV gp-R) (see Abstract). The teaching provides a displayed EGF as an extension of the N terminus of GaLV surface unit gp-R and an investigation of its effects on EGF positive and negative cells (see Abstract). The authors found that virus-cell infectivity of the GaLV gp-R vector was restricted to EGF receptor-positive cells (see whole document). The gene, vector, cell lines and infection assays are described within the Material and Methods (see pages 818-821). Of note, the GaLV is a membrane glycoprotein and incorporating either an EGF or IGF-I leads to cell to cell fusion; thus, the protein would be expected to be distributed among a cell's outer

membrane. The authors conclude that the specificity of GaLV gp can be regulated by N-terminal display of ligands, resulting in altered viral tropism (see Abstract and Discussion). This reference provides no teaching with respect to TAG72 proteins.

Goel et al describe an ScFv of the pancarcinoma monoclonal antibody CC49 (see Abstract). The murine MAb CC49 recognizes the tumor-associated glycoprotein, TAG72 (see Abstract). The authors report genetic engineering and *in vivo* evaluation of a tetravalent scFv construct of MAb CC49. The authors claim that this tetravalent construct shows an improvement in binding properties compared to that of the dimer and the CC49 IgG (see Introduction). Further, this construct has a longer half-life in blood than divalent scFv (see Discussion).

Thus, it would have been obvious for one of ordinary skill in the art to combine the teachings of the references above in order to make a fusion protein comprising the GaLV gp (as taught by Fielding et al) and the ScFv as engineered by Goel et al. One would have been motivated to do so, given the known cell-killing capacity of GaLV gp as well as the ability to alter its tropism. One would have also been motivated to incorporate the ScFv construct as taught by Goel, given its improved binding properties to TAG72, or tumor-associated gp, and its longer half-life. There would have been a reasonable expectation of success because of the demonstrated successes in both teachings. Further, the underlying techniques are commonly used and widely known. The invention as a whole was clearly *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

NO CLAIM IS ALLOWED.

Claims 2, 3, 5 and 7 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. The sequences set forth in SEQ ID NOs: 8, 9 and 10 are free of the prior art.

Comment [BC3]: Use FP 7-43 for this - you have the right idea, but you are not giving enough info. John L is a stickler for using the correct FPs!

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MICHELLE HORNING whose telephone number is (571)272-9036. The examiner can normally be reached on Monday-Friday 8:00-5:00 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michelle Horning/
Examiner, Art Unit 1648

/Bruce Campell/
Supervisory Patent Examiner, Art Unit 1648